REMARKS/ARGUMENTS

Specification

The specification has been amended to provide a description of the deposited biological material sufficient to specifically identify it, in compliance with CFR 1.809(d)(3). Applicant submits that the specification as amended complies with CFR 1.809(d)(1-4). No new matter has been added by way of the amendment.

Claims

Claims 16-28 are currently pending. Claims 16, 17, and 22-27 have been withdrawn as drawn to a non-elected invention. Claims 18 and 21 have been amended. Claim 28 has been added.

Claims 18 and 21 have been amended to recite that the monoclonal antibody is of human origin. Claim 21 has also been amended to correct a grammatical error. New claim 28 is directed to a monoclonal antibody produced by the method of claim 21. Support for the claim amendments and new claim 28 can be found throughout the specification. No new matter has been added by way of the amendments.

Statement by an Attorney of Record

Applicant submits herewith a copy of the receipt for the deposit of IA-2, 96/3/1, under deposit number DSM ACC2365, and a statement by an attorney of record, stating that the specific cell line has been deposited under the Budapest Treaty, that the cell line will be released to the public upon issuance of a patent, and that the cell line will be replaced should it ever become non-viable.

Associate Power of Attorney

Applicant submits herewith an associate Power of Attorney for the law firm of McDonnell, Boehnen, Hulbert & Berghoff (Customer Number 020306) from an attorney

or agent of record. Accordingly, Anita Terpstra is an attorney of record via the associate Power of Attorney document.

Discussion of the 35 U.S.C. § 112 Rejections

(Paragraph 3 of the Office Action)

Claims 18-20 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse the rejection.

The Office alleges that the specification fails to provide an adequate written description of the invention and fails to provide an enabling disclosure because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or (3) deposited in compliance with the criteria set forth in 37 CFR §§1.801-1.809.

Applicant provides herewith evidence of a deposit of the claimed biological material under the terms of the Budapest Treaty and in compliance with CFR §§1.801-1.809. Specifically, Applicant submits herewith: (1) a copy of the receipt for the deposit of IA-2, 96/3/1 (deposit number DSM ACC2365), made on August 13, 1998 at the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH ("DSMZ"), which is approved as an International Depository Authority under the Budapest Treaty (see Exhibit "A"); (2) a copy of the viability statement issued by the DMSZ for deposit number DSM ACC2365 (see Exhibit "B"); (3) general information regarding the DSMZ, indicating that it is an approved depository under the Budapest Treaty (see Exhibit "C"); and (4) a statement by an attorney of record stating that the claimed cell line has been deposited under the Budapest Treaty, that the cell line will be released to the public upon issuance of a patent, and that the cell line will be replaced should it ever become non-viable.

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Furthermore, Applicant has amended the specification to include complete deposit information for the claimed monoclonal antibody in compliance with the criteria set forth in 37 CFR §§1.801-1.809.

In view of the fact that Applicant has deposited the claimed biological material in compliance with the criteria set forth in 37 CFR 1.801-1.809, Applicant respectfully requests withdrawal of the rejection.

(Paragraph 4 of the Office Action)

Claims 18-20 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Office action maintains that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, The Office Action alleges that even though the specification defines the binding properties of the claimed monoclonal antibodies as having a detectable epitope overlap with a defined known antibody, the specification does not disclose any characteristics of (and therefore lacks any description of) the antibody being claimed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., id.* at 1116; M.P.E.P § 2163(I). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the

adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976); *Ex parte Sorenson*, 3 USPQ2d 1462 (Bd. Pat. App. & Int. 1987); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; (5) and the method of making the claimed invention. M.P.E.P. §2163(II)(A)(3)(a)(i)(C)(2). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient to satisfy written description. *Id*; *see Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406. Further, the written description requirement does not require an actual reduction to practice. M.P.E.P. § 2163.

Contrary to the Office's allegation, the specification thoroughly describes the characteristics of the claimed monoclonal antibody. For example, the specification teaches that the monoclonal antibody against IA-2 is preferably from the IgG sub-type (specification at, e.g., pages 6 and 19). In addition, the specification clearly teaches the binding characteristics of the claimed monoclonal antibody. For example, the specification teaches that the monoclonal antibody binds specifically to islet cell antigen IA-2 (throughout the specification and particularly at, e.g., pages 4-5, 10-12, and 15-17). The specification further teaches the physical and chemical characteristics of antigen IA-2. For example, the specification teaches, among other things, that IA-2 is a protein tyrosine phosphatase containing a transmembrane domain and a cytoplasmic domain (IA-2ic) which contains the epitopes for antibody binding (specification at, e.g., pages 2-3,

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

12-14). In addition, the physical/chemical characteristics of IA-2 were known in the art and described by others (see, e.g., Solimena et al, EMBO J., 15: 2101-2114 (1996); Payton et al., J. Clin. Invest., 96: 1506-1511 (1995); Zhang, et al., Diabetes, 46: 40-43 (1997)).

The specification further teaches the antigenic epitope recognized by the claimed monoclonal antibody and specifies its binding requirements. Specifically, the specification teaches that the claimed monoclonal antibody recognizes the cytoplasmic domain of IA-2 antigen (IA-2ic) and provides methods for confirming the binding specificity. For example, the specification teaches that the claimed monoclonal antibody has equivalent binding, i.e., detectable epitope overlap, with that of an antibody from cell line IA-2 deposit number DSM ACC 2365 (specification at, e.g., pages 4-5, 10-11). The specification teaches that an antibody from deposit number DSM ACC 2365 binds to the cytoplasmic domain of IA-2 antigen (IA-2ic) (specification at, e.g., pages 4-5, 10-12) and provides the requisite deposit information for DSM ACC 2365 (specification at pages 5, 10). (Applicant points out that the Federal Circuit has held that reference to a deposit in a public depository, which makes its contents accessible to the public, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002)). The specification further teaches methods for testing the binding specificity of the claimed monoclonal antibody, i.e., confirming the epitope overlap with DSM ACC 2365 (specification at, e.g., pages 10-11, 13-15).

The specification also clearly teaches that the function of the claimed monoclonal antibody is to specifically bind to islet cell antigen IA-2, preferably the cytoplasmic domain of IA-2 (IA-2ic) (specification at, e.g., pages 2-4, 10-12) and provides several uses for the claimed monoclonal antibody.

In addition to teaching the binding characteristics and function of the claimed monoclonal antibody, the specification also contains a thorough description of how to make the claimed monoclonal antibody (e.g., pages 6-9, 11-15). For example, the specification teaches the selection of appropriate donor lymphocytes from prediabetic or

diabetic donors with high IA-2-specific serum antibody titres (specification at, e.g., pages 6 and 18). The specification further describes how to select for such donors and provides exemplary methods for the selection of donors (specification at, e.g., pages 6 and 18). In addition, the specification teaches further methods for the production of the claimed monoclonal antibodies, including pre-selection for IgG-producing B lymphocytes (e.g., pages 6-7 and 19), immortalization of IA-2-specific B lymphocytes (e.g., pages 7, 9-10, and 19-20), cell culture methods for optimal growth of immortalized IA-2-specific B lymphocytes (e.g., pages 7-8), cloning methods for the optimal production of IA-2-specific B lymphocytes (e.g., pages 7-9, and 22), and screening methods to produce IA-2-specific B lymphocytes (e.g., pages 8, 13-15, and 21-22). The specification further teaches methods for testing the binding specificity of the claimed monoclonal antibody (specification at, e.g., pages 10-11, 13-15).

Applicant further points out that the disclosure obligation varies according to the art to which the invention pertains. *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F.2d 1527, 1534-35, 25 U.S.P.Q.2d 1241, 1246 (Fed. Cir.1992). Thus, the Patent Office's internal guidelines assert that in certain instances, "the written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function." M.P.E.P. § 2163(II)(A)(3)(a)(i)(C)(2). With respect to monoclonal antibody art, the Patent Office has clearly stated that antibody technology is well-developed and that the correlation between antibody structure and function are well-characterized. Specifically, the Synopsis of Application of Written Description Guidelines provides that the Patent Office should find that a claim directed to "any antibody which is capable of binding to antigen X" complies with the written description requirement, notwithstanding the functional definition of the antibody, in view of "the well-defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well-developed and mature." *Synopsis of Application of Written Description Guidelines*, at 59-60 (http://www.uspto.gov/web/patents/guides.htm). In other words, according to the

reasoning of the written description guidelines, as long as the antigen is characterized, an antibody that binds to that antigen satisfies the written description requirement because the structure of antibodies is well known in the art and the correlation between antibody structure and function is well-characterized. *Synopsis of Application of Written Description Guidelines*, at 59-60.

In addition, a recent decision by the Federal Circuit has confirmed the PTO guidelines. The *Enzo* court held that the written description requirement is met if a description of the functional characteristic(s) is coupled with a correlation between the described functional characteristic(s) and a structure that is sufficiently known or disclosed, i.e., such as the structure of an antibody. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). In the present case, the application satisfies the written description requirement because the functional characteristics of binding to islet cell antigen IA-2 in a manner equivalent to that of an antibody from deposit number DSM ACC2365 (i.e., binding to the cytoplasmic domain IA-2-ic) is coupled with a correlation between the described binding characteristics and the well-known structure of an antibody.

In view of the fact that the IA-2 antigen is well-characterized in the specification and in the art, and based on the teachings in the specification of the binding characteristics of the claimed monoclonal antibody, its functional characteristics, the well-established correlation between antibody structure and function, and the methods of making the claimed monoclonal antibodies, as outlined above, Applicant has clearly described identifying characteristics that distinguish the claimed monoclonal antibody, such that one skilled in the art would conclude that Applicant was in possession of the claimed invention.

Despite these teachings, the Office Action alleges that it would require undue experimentation for one skilled in the art to make and use the claimed antibodies because the claimed monoclonal antibody has not been properly described and because the prior art teaches that microheterogeneities are common in the production of monoclonal antibodies. For all of the reasons provided above, Applicant submits that the monoclonal

antibody has been properly described. Furthermore, under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to make and use a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. The test for enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

Contrary to the Office's allegation, the instant specification provides considerable guidance to enable a skilled artisan to make and use a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. For example, the specification fully describes the binding characteristics of a monoclonal antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365, including its binding properties to the cytoplasmic domain of IA-2ic of islet cell IA-2 (specification at, e.g., pages 4-5, 10-12). The specification further describes a monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365 at, e.g., pages pages 4-5 and 10-11. As described, the claimed monoclonal antibody is one that has detectable epitope overlap with an antibody from deposit number DSM ACC2365.

In addition, the specification fully teaches one skilled in the art how to make a monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. For example, as outlined in detail above, the specification teaches one skilled in the art how to make a monoclonal antibody that binds to islet cell antigen IA-2, including, for example, an antibody from deposit number DSM ACC2365 (see above discussion). The specification further teaches one skilled in the art how to test the

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

monoclonal antibody to determine that it binds in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. For example, the specification teaches assays, such as competition assays, to confirm the binding specificity of the claimed monoclonal antibody (specification at, e.g., pages 10-11, 13-15).

The specification also fully teaches one skilled in the art how to use the claimed monoclonal antibody. For example, the specification teaches that auto antibodies against IA-2 are associated with the rapid progression of insulin-dependent diabetes mellitus (IDDM) and can be used as a marker for IDDM (specification at page 2). Thus, the specification teaches that the claimed monoclonal antibody against IA-2 can be used as standard or calibration material or as a receptor in a diagnostic assay for the quantitative detection of IA-2-specific autoantibodies (specification at pages 4 and 15-16). In addition, the specification teaches that the monoclonal antibody of the invention can also be used in assays to isolate the islet cell antigen IA-2 and provides exemplary assays for use (specification at pages 16-17).

Despite these teachings, the Office Action alleges that it would require undue experimentation for one skilled in the art to make and use the claimed antibodies because the prior art teaches that microheterogeneities are common in the production of monoclonal antibodies. Specifically, the Office cites Ackerman to argue that the deposit of one particular monoclonal antibody does not enable a monoclonal antibody with similar properties because the replication of a specific monoclonal antibody is an unpredictable event. However, the Office mischaracterizes the Ackerman article. Ackerman is directed to an investigation of the *postsecretory effects* on monoclonal antibodies under different tissue culture conditions and reports the potential of some mammalian and insect cell lines to degrade (i.e., via proteolysis) or modify (i.e., glycosylate, sialylate) a human monoclonal antibody once it is formed and released into the supernatant (page 97, right column, last paragraph). Such postsecretory effects do not influence the initial production or antigenicity of the monoclonal antibody because they occur *after* production of the antibody (i.e. after antigenic screening). Further,

microheterogeneities that arise from variation in postsecretory effects can apparently be controlled by maintaining consistent culture conditions. Importantly, although Ackermen mentions that others have observed the occurrence of microheterogeneities in monoclonal antibodies, Ackerman's own group found no microheterogeneities that interfered significantly with the ability of the antibody to recognize its specific antigen (page 101, left column, last paragraph to right column, first paragraph).[1]

Furthermore, even with the existence of microheterogeneities, Applicant respectfully submits that one skilled in the art would be able to produce the claimed monoclonal antibody without undue experimentation based on the teachings in the specification. In addition to clearly teaching one skilled in the art how to make the claimed monoclonal antibody, the specification clearly teaches one skilled in the art how to test the produced monoclonal antibody to determine that it has the appropriate binding characteristics. Applicant submits that it is a matter of routine experimentation to screen monoclonal antibodies for the appropriate binding characteristics using the techniques described in the specification and other well-known techniques. The law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Further, the fact that experimentation may be complex does not necessarily make it undue. *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is unduly extensive. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *In re Angstadt*, 537 F.2d 498 (CCPA 1976). In the antibody field, experimentation is not considered undue if a skilled artisan has to make several attempts before achieving success in producing a suitable antibody. *Johns Hopkins University v.*

[1] Specifically, Ackerman reports as follows: "Finally, the capacity of the antibody for specific binding of the antigen was investigated by an erythrocyte-binding test based on agglutination. In all samples, agglutination of erythrocytes was observed at the same dilution of 1:500 to 1:1000, which was identical to the initial antibody preparation and indicates that none of the culture media with or without microcarriers interfered significantly with the ability of the antibody to recognize its specific antigen."

CellPro, Inc., 47 USPQ2d 1705 (Fed. Cir. 1998) ("[R]outine repetition of a patent's specification to achieve a desired experimental result does not constitute undue experimentation."). Applicant submits that, based on the teachings in the specification, producing the claimed monoclonal antibody and screening it to confirm its binding specificity would be well within the knowledge and skill of the ordinary artisan and would not involve undue experimentation.

In this regard, Applicant points out that several cases decided by the Federal Circuit and the Board of Patent Appeal and Interferences have held that screening hybridomas for monoclonal antibody production is conventional and routine. For example, the Court in In re Wands found that screening hybridomas was routine, reasoning that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); see also *Staehashelin v. Secher*, 24 USPQ2d 1513 (BdPatApp&Int); *Ex parte Erlich*, 3 USPQ2d 1011 (BdPatApp&Int); *Johns Hopkins University v. CellPro, Inc.*, 47 USPQ2d 1705 (Fed. Cir. 1998). Further, none of these Courts limited the scope of the claims to the deposited material. For example, the Court in *Johns Hopkins University v. CellPro, Inc.* found that a claim drawn to the genus of antibodies which bind to the claimed antigen is enabled, even though the specification disclosed only the method of producing one antibody to the claimed antigen. 47 USPQ2d 1705 (Fed. Cir. 1998). Likewise, the Board in *Staehashelin v. Secher,* found that a claim reciting a monoclonal antibody capable of specifically binding to at least one antigenic determinant of interfereon-α was enabled and satisfied the written description requirement because the law did not require the exact exemplification or details for preparing every species within the described genus. 24 USPQ2d 1513 (BdPatApp&Int). Accordingly, the Federal Circuit and the Patent Office maintain that a claim to a genus of monoclonal antibodies is enabled by a description of the production of a species because it is within the skill of an ordinary artisan to produce

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

and screen hybridomas based on teachings in the specification to achieve a monoclonal antibody having the desired binding properties.

For all of the reasons discussed above, the claims satisfy the written description and enablement requirements. Accordingly, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 112 rejections.

Discussion of the 35 U.S.C. § 102(e) Rejection

Claims 18-21 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Endl et al. This rejection is respectfully traversed for the reasons set forth below.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881 (S.D. Ind.1993) ("A patent is anticipated only if all the elements and limitations of the claims are found within a single, prior art reference."); *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984); M.P.E.P § 2131. Furthermore, no difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881 (S.D. Ind.1993). Also, the identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

To anticipate claims 18-21, the Endl patent must teach each and every element as set forth in the claims, that is, the Endl patent must teach a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. Furthermore, the Endl patent must describe the claimed invention in as complete detail as is contained in the present claims. However, the Endl patent discloses monoclonal antibodies that bind to

islet cell antigen glutamic acid decarboxylase (GAD) (see col. 2, lines 29-31 and col. 4, lines 3-8) and fails to even mention a monoclonal antibody that binds specifically to islet cell antigen IA-2. Further, given that the method taught in the Endl patent is for the production of monoclonal antibodies that bind to islet cell antigen GAD, the Endl patent necessarily fails to teach a method for producing a monoclonal antibody that binds specifically to islet cell antigen IA-2 (claim 21). For example, the Endl patent fails to teach the step of isolating peripheral mononuclear cells (PBMNC) from the blood of a human donor having a high serum antibody titre of IA-2. Moreover, given that the Endl patent fails to teach the pursuit of a monoclonal antibody against IA-2, it further fails to teach steps (d)-(f) of claim 21. Thus, the Endl patent does not anticipate present claims 18-21 because it fails to describe each and every element as set forth in the claims in as complete detail as is contained in the claims.

The Office argues that Endl discloses human monoclonal antibodies of the IgG isotype against human pancreatic islet cells and methods for making the same. However, the Federal Circuit clearly states that the *identical invention* must be described or shown *in as complete detail* as is contained in the claim. Although the Endl patent discusses human monoclonal antibodies against human pancreatic islet cells in general, it describes in detail only those monoclonal antibodies that bind to islet cell antigen GAD. Thus, the Endl patent fails to describe the identical invention, i.e., a monoclonal antibody that binds specifically to islet cell antigen IA-2, in as complete detail as is contained in the claims. Likewise, although the Endl patent discusses a general method for producing monoclonal antibodies against human pancreatic islet cells, it fails to describe the identical method for producing a monoclonal antibody that binds specifically to islet cell antigen IA-2 in as complete detail as is contained in claim 21.

For the reasons set forth above, the Endl patent does not anticipate the present claims. Accordingly, withdrawal of the 35 U.S.C. § 102(e) rejection based on Endl is respectfully requested.

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Discussion of the 35 U.S.C. § 102(b) Rejection

The Office rejected claims 18-20 under 35 U.S.C. § 102(b) as allegedly being anticipated by Solimena et al., EMBO J., 15: 2102-2114 (1996). The rejection is respectfully traversed.

Under 35 U.S.C. §102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 10533 (Fed. Cir. 1987); *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881 (S.D. Ind.1993). Furthermore, no difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *In re Recombinant DNA Technology Patent and Contract Litigation*, 30 USPQ2d 1881 (S.D. Ind.1993). Thus, in order for a prior art reference to anticipate the claimed invention, the prior art reference must identically disclose the claimed invention. *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 780 (Fed. Cir. 1985). See also, *Azko N.V. v. U.S. International Trade Commission*, citing In re Arkley, 455 F.2d 586, 587 (CCPA 1972) (The anticipatory reference must disclose in the prior art a thing substantially identical with the claimed invention); *Ex parte Kung*, 17 USPQ2d 1545, 1548 (Bd Pat App & Int 1989) (To anticipate, the prior art invention must reasonably appear to be either identical with or only slightly different than the claimed invention); *University of California v. Eli Lilly and Co.*, 39 USPQ2d 1225, 1242 (S.D. Ind. 1995) (No difference may exist between the claimed invention and the reference disclosure). Furthermore, the identical invention must be described or shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); *Chester v. Miller*, 15 USPQ2d 1333 (Fed. Cir. 1990); M.P.E.P. § 2131.

To anticipate claims 18-20, Solimena et al must teach a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1, deposit number DSM ACC2365. Furthermore, Solimena et al. must describe the claimed invention in as complete detail as is contained in the present claims. The Office alleges that Solimena et al anticipates the present

invention because it teaches monoclonal antibodies that can bind to IA-2. However, in contrast to the present claims which are directed to *human* monoclonal antibodies, the teaching in Solimena et al is limited to the description of two *mouse* monoclonal antibodies derived from immunized mice. Given that Solimena et al fails to describe each and every element as set forth in the claims in as complete detail as is contained in the claims, Solimena et al fails to anticipate the present claims.

Further, to anticipate claims 18-20, Solimena et al. would have to *identically disclose* a human monoclonal antibody that binds specifically to islet cell antigen IA-2. However, as discussed above, Solimena et al discloses a mouse monoclonal antibody and thus fails to *identically disclose* the human monoclonal antibody of the present invention.

Also, the prior art reference must provide an enabling disclosure. M.P.E.P. §2121.01; *In re Hoeksema*, 399 F.2d 269 (CCPA 1968) ("In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention' 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ."). It is well-established by the Federal Circuit that "even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000) (quoting *In re Donohoe*, 766 F.2d 531, 533 (Fed Cir. 1985); see also *Ex parte Thomsom*, 24 USPQ2d 1618 (Fed. Cir 1992); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, USPQ 649 (Fed. Cir. 1986); *Azko N.V. v. U.S. International Trade Commission*, 1 USPQ2d 1241 (Fed Cir. 1986); *In re Borst*, 345 F.2d 851, 855 (CCPA 1965); *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962) (the mere description of an invention is not necessarily an "enabling" disclosure; such descriptions must be capable of placing the invention in the possession of those skilled in the art). A disclosure is enabling if a person of ordinary skill in the art could have made or obtained the claimed invention without an undue amount of experimentation. *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000) (citing *In re Sheppard*, 339 F.2d 238, 242 (CCPOA 1981).

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

In other words, a reference must describe the subject matter of the claimed invention sufficiently to have placed it in possession of the public through an enabling disclosure. *Helifix Ltd. v. Blok-Lok, Ltd.*, 54 USPQ2d 1299 (Fed. Cir. 2000) (citing *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994); *Ex parte Thomsom*, 24 USPQ2d 1618 (Fed. Cir 1992); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, USPQ 649 (Fed. Cir. 1986); *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *In re Sasse*, 629 F.2d 675, 681 (CCPA 1980); *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962); M.P.E.P. §2121.01. To place the invention in the possession of the public, the reference must be "so precise and so particular that any person skilled in the art to which the invention belongs can construct and operate it without further experiments and without further exercise of inventive skill." *In re LeGrice*, 301 F.2d 929, 934 (CCPA 1962) (quoting I Robinson on Patents, Sec. 325 (1890)); *In re Brown*, 141 USPQ 245, (CCPA 1964).

Solimena et al fails to provide an enabling disclosure such that one skilled in the art could produce the claimed human monoclonal antibodies without further experiments and without further exercise of inventive skill. First, the teaching in Solimena et al. is limited to the production of mouse monoclonal antibodies and fails to teach the production of human monoclonal antibodies. Second, given that Solimena et al. fails to provide any methods or guidance whatsoever for the production the mouse monoclonal antibodies, it certainly fails to provide guidance for the production of the claimed human monoclonal antibodies. In fact, the teaching in Solimena et al. is limited to the following single sentence: "Anti-ICA 512 monoclonal antibodies 257.1 and 257.4 were generated by immunizing mice with the glutathione S-transferase (GST)-ICA 512 fragment including amino acids 643-979." Such limited teaching certainly does not amount to a "precise and particular" disclosure for the production of the claimed human monoclonal antibodies.

Even if, for the sake of argument, one presumed that the authors of the Solimena et al reference used routine methods of immunization and hybridoma production to produce the described mouse monoclonal antibodies, such routine methods would *not* have enabled one skilled in the art to produce the claimed human monoclonal antibodies.

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

As explained in the specification, monoclonal antibodies that specifically bind to islet cell antigen IA-2 can not be produced using routine hybridoma methods. For example, among other things, the donor lymphocytes must be derived from selective pre-diabetics or diabetics with high IA-2-specific serum antibody titres (see, e.g., specification at page 6). Also, it is advantageous to pre-select for IgG-producing B lymphocytes (specification at page 6). Furthermore, the specification teaches novel methods for the successful culture and cloning of immortalized IA-2-specific B lymphocyte cells (specification at pages 7-10). Given that the claimed monoclonal antibodies can not be produced using routine hybridoma methods for the production of mouse monoclonal antibodies, one skilled in the art could not have produced the claimed human monoclonal antibodies based on Solimena et al. without further experiments and without further exercise of inventive skill and ingenuity.

For the reasons set forth above, withdrawal of the 35 U.S.C. § 102(b) rejection based on Solimena et al. is respectfully requested.

Discussion of the 35 U.S.C. § 103 Rejection

The Office rejected claims 18-20 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Payton et al. (J. Clin. Invest., 96: 1506-1511 (1995)), in view of Kohler et al. (Science, 233: 1281-1286 (1986)). The rejection is respectfully traversed.

Claims 18-20 are directed to a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2, 96-3-1. Thus, to establish a *prima facie* case of obviousness, the Office must show: (1) a teaching or suggestion to make a human monoclonal antibody that binds specifically to islet cell antigen IA-2 in a manner equivalent to that of an antibody from cell line IA-2; and (2) a reasonable expectation of success of making such a monoclonal antibody. The teaching or suggestion to make a monoclonal antibody that binds specifically to islet cell antigen IA-2 with the recited binding properties and the reasonable expectation of its success must both be found in the prior art, and must not be based on applicant's

disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Dance*, 160 F.3d 1339 (Fed. Cir. 1998); M.P.E.P. § 2143.

Neither of the cited references, alone or in combination, teach or suggest a human monoclonal antibody that binds specifically to IA-2. Payton et al. merely reports the identification of a 40,000 M_r protein fragment found in patients with insulin-dependent diabetes mellitus (IDDM) believed to be derived from a protein similar to or identical with IA-2. Payton et al. fails to even mention the production of monoclonal antibodies, much less teach or suggest a monoclonal antibody that binds specifically to IA-2.

Kohler et al. fails to cure the deficiencies of Payton et al. Kohler et al. merely teaches a general method for the production of mouse monoclonal antibodies. The method of Kohler et al is limited to the production of mouse monoclonal antibodies using mouse myeloma tumor cells fused to spleen cells derived from a mouse that has previously been immunized with antigen. Kohler et al offers no further teaching for alternative methods of producing monoclonal antibodies and certainly offers no teaching or suggestion for the production of *human* monoclonal antibodies. Furthermore, given that Kohler et al does not even contemplate making a monoclonal antibody that binds specifically to islet cell antigen IA-2, it certainly does not teach or suggest to make the monoclonal antibody of the present invention.

The Office Action alleges that "it would have been obvious to one of ordinary skill in the art ... to produce a monoclonal antibody against the IA-2 taught by Payton using the method of Kohler because Kohler teaches that any substance that can elicit a humoral response can be used to prepare monoclonal antibodies, and that monoclonal antibodies provides advantages not found in polyclonal antibodies." (Office Action, page 8). However, contrary to the Examiner's contention, one skilled in the art would not have been motivated to combine the teachings of Payton et al and Kohler et al. to produce a *human* monoclonal antibody against IA-2 antigen. First, Payton et al. provides no suggestion whatsoever to pursue a human monoclonal antibody against IA-2. Second, even if for the sake of argument, Payton et al. provided a suggestion to pursue a human monoclonal antibody against IA-2, one skilled in the art would not have been motivated

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

to seek the teachings of Kohler et al. As discussed above, Kohler et al. teaches the production of mouse monoclonal antibodies using mouse myeloma tumor cells which are fused to spleen cells derived from a mouse that has been immunized with antigen. As noted by the Examiner (above), the method of Kohler requires immunizing a mouse with an antigen so as to elicit a humoral response. Such method requires sufficient quantities of antigen for immunization. Given that Payton et al teaches that the IA-2 antigen is expressed at low levels in pancreatic islet and insulinoma cells and further teaches the difficulty of obtaining IA-2 protein (page 1506, right column, lines 15-18), one skilled in the art would not have been motivated to seek the teachings of a method that requires a sufficient quantity of isolated protein/antigen for immunization. Accordingly, one skilled in the art would not have been motivated to combine the teachings of Payton et al and Kohler et al.

Furthermore, even if for the sake of argument, there was motivation to combine the teachings of Payton et al and Kohler et al, one skilled in the art would have no reasonable expectation of success of producing a *human* monoclonal antibody that specifically binds to IA-2 antigen based on the combined teachings of these references. As discussed above, Kohler et al. teaches a method for producing a mouse monoclonal antibody by immunizing a mouse with the antigen of interest. Subsequently, the spleen of the immunized mouse is removed and the spleen cells are fused with mouse myeloma tumor cells. However, the production of mouse monoclonal antibodies described by Kohler is fundamentally different from the production of human monoclonal antibodies and could not be used to produce the claimed monoclonal antibodies for several reasons. First, as discussed above, it would be difficult to obtain a sufficient quantity of IA-2 antigen for immunization given that IA-2 antigen is present at low levels in islet and insulinoma cells. Second, even if one could obtain a sufficient amount of IA-2 antigen, it is not feasible to immunize a human to raise antibodies for several reasons, including the fact that the availability of antibody producing human lymphocytes in peripheral blood is low. Third, the Kohler reference fails to teach cell culture methods for immortalizing, cloning, and growing the mouse hybridoma cells, and certainly does not teach cell culture

methods for developing human hybridoma cells. Given that mouse cells and human cells have different properties and different growth requirements, they each have different cell culture requirements. Accordingly, cell culture media and methods used to grow mouse lymphocytes would not be successful to promote the growth of human lymphocytes in culture. Thus, even if immunization of humans and retrieval of antibody producing human lymphocytes was feasible, and even if the Kohler reference taught cell culture methods for mouse lymphocytes, there still would not have been a reasonable expectation that the antibody-producing human lymphocyte could be successfully immortalized, cultured and cloned to produce the monoclonal antibody of the present invention.

For the reasons set forth above, the prior art references do not disclose, either individually or in combination, a human monoclonal antibody that specifically binds IA-2 antigen. Accordingly, Applicant respectfully requests withdrawal of this rejection.

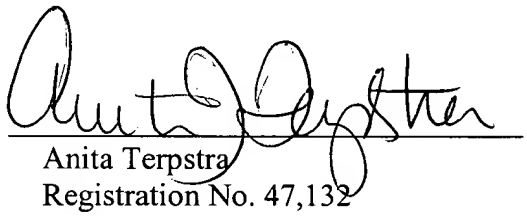
McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of this application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: November 14, 2003

By: 
Anita Terpstra
Registration No. 47,132

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

EXHIBIT A

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Boehringer Mannheim GmbH
Sandhofer Str. 116

68305 Mannheim

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
IA-2, 96/3/1/1	DSM ACC2365

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I. above was accompanied by:

(X) a scientific description
( ) a proposed taxonomic designation

(Mark with a cross where applicable).

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I. above, which was received by it on 1998-08-13 (Date of the original deposit)[1].

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion).

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiss Date: 1998-09-04

[1] Where Rule 6.4 (d) applies, such date is the date on which the status of international depositary authority was acquired.

EXHIBIT B

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

Boehringer Mannheim GmbH
Sandhofer Str. 116

68305 Mannheim

VIABILITY STATEMENT
issued pursuant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: Boehringer Mannheim GmbH Sandhofer Str. 116 Address: 68305 Mannheim	Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY: DSM ACC2365 Date of the deposit or the transfer[1]: 1998-08-13

III. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on 1998-08-13 [2].
On that date, the said microorganism was

(X)[3] viable

( )[3] no longer viable

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED[4]

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: DSMZ-DEUTSCHE SAMMLUNG VON MIKROORGANISMEN UND ZELLKULTUREN GmbH Address: Mascheroder Weg 1b D-38124 Braunschweig	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): U. Weiss Date: 1998-09-04

[1] Indicate the date of original deposit or, where a new deposit or a transfer has been made, the most recent relevant date (date of the new deposit or date of the transfer).
[2] In the cases referred to in Rule 10.2(a) (ii) and (iii), refer to the most recent viability test.
[3] Mark with a cross the applicable box.
[4] Fill in if the information has been requested and if the results of the test were negative.

Form DSMZ-BP/9 (sole page) 0196

EXHIBIT C

Patent and Safe Deposit DSMZ

General Information on the Deposit of Biological Material for Pat nt Purposes

To achieve patent protection for an invention, a full disclosure of the process in question must be given to enable a person skilled in the art to practice the invention. This is usually done through means of a written description. As biological material involved in biotechnological inventions cannot be described in such a way that they are "reworkable", patent offices of most countries require that the organism must be deposited with a recognized independent public culture collection.

Budapest Treaty

Since 1981 patent deposits are regulated internationally through the 'Budapest Treaty (pdf) on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure' (obtainable from WIPO, World Intellectual Property Organization, Geneva) to overcome the difficulties arising from the differing national patent regulations. Further information about where and how to deposit may be drawn from the "Guide to the Deposit of Microorganisms under the Budapest Treaty" (WIPO, Geneva, ISBN 92-805-0195-X). A list of the countries being member to the Budapest Union and of the collections which have been recognized as International Depositary Authorities (IDAs) may be found in the January issue of 'Industrial Property and Copyright', a monthly Journal of WIPO.

The main facts for a deposit according to the Budapest Treaty can be concluded as follows:

- A deposit with an IDA (the DSMZ) is recognized as valid by all Contracting States of the Budapest Union.
- Storage time is at least 30 years.
- After deposition the culture cannot be claimed back.
- The depositor should himself keep samples of the culture for the same period of time, so that -in case the culture is for any reason no longer available from the Depositary Authority- he can replenish the stock.
- The Depositary Authority (the DSMZ) is obliged to keep secrecy about the fact of a deposit and the nature of the deposited material.

DSMZ Patents and Safe Deposit

Deposit of Human and Animal Cell Cultures for Patent Purposes

DSMZ

- The DSMZ was approved as International Depository Authority under the Budapest Treaty of 1977 for animal and human cell cultures by the World Intellectual Property Organization on 28 February 1991.

- The form DSMZ-BP/1-Animal and Human Cell Cultures 09/2000 must be completed and submitted to the DSMZ together with information regarding delivery at least 72 hours before dispatch. The form requests the name and address of the depositor, an identification reference of the cell culture, a listing of properties of the material which may be hazardous to health or environment (potential pathogenicity), an indication whether and how the cells have been genetically manipulated, and details for cultivation and storage of the material.

- Cell cultures (including hybridomas) are accepted on the condition that they can be preserved without significant change or loss of properties by freezing and long-term storage. Deposits are only accepted in the form of frozen ampoules. The DSMZ requires 12 ampoules (all prepared at the same time) containing at least 5 x 10E6 cells per ampoule (cells growing in suspension) and 2 x 10E6 cells per ampoule (adherent cells). It is the responsibility of the depositor to furnish sufficient quantity for the specified period of time and to replenish the stock if cell cultures should be destroyed during the effective life of the patent.

- Deposits under the Budapest Treaty must be tested for viability. The DSMZ will examine at least one ampoule for viability and possible contamination by other organisms (in particular by mycoplasmas). This procedure usually requires about two weeks. It is advisable to submit cell cultures grown in medium free from any antibiotics which might mask a latent infection. Non-viable or infected cell cultures will not be accepted for patent deposit. In the case of deposit rejection, the costs of the tests will be charged to the depositor.

- On final acceptance, the DSMZ will hold the deposits under the terms and conditions of the Budapest Treaty for 30 years. The DSMZ will issue written Statements of Acceptance and of Viability. The date of receipt becomes the deposit date. A DSMZ number will be assigned to the cell culture.

- The depositor must pay the statutory fee; an invoice will be sent after the deposition formalities are completed. The depositor is responsible for transportation costs ensuing from delivery of deposits to the DSMZ. An appropriate amount of dry ice for the period of transportation should be used. The imminent delivery should be announced to the DSMZ. Please, ensure delivery to Braunschweig ("door-to-door") and not for instance only to the airport in Hannover.

- Click here for general information on patent deposit, for further technical questions contact and address package to:

Dr. H. Quentmeier
DSMZ - Department of Human and Animal Cell Cultures
Mascheroder Weg 1B
D-38124 Braunschweig, Germany
Tel: +49-531-2616.165
Fax: +49-531-2616.150
E-Mail: hqu@dsmz.de

Mycoplasma Elimination in Patent Cell Lines

Cell lines contaminated with mycoplasma cannot be accepted for patent deposit. We offer the service of mycoplasma elimination (for price see the current Price List). Contaminated cell cultures will be treated with antibiotics active against mycoplasmas. Our success rate is in the range of 70-85% of the cultures; the remaining percentages refer to cultures remaining mycoplasma positive (resistant strains or development of resistance) or cell cultures lost due to cytostatic or cytotoxic effects of the reagents. In order to ensure that indeed long-term cleansing of the cultures has occurred, the cell lines will be subjected to rigorous retesting using at least two sensitive and reliable methods (e.g. agar colonies, DNA-RNA hybridization, PCR analysis). We cannot give any guarantee for successful treatment of mycoplasma infection. As, however, any treatment involves a large amount of work, reagents and time, we must ask for reimboursement of 50% of the full price of mycoplasma elimination in the

case of a failed attempt.

For references detailing the methods used at the DSMZ for mycoplasma detection and treatment, see Mycoplasma Detection and Elimination .